Program Announcements (PA'S)

MOLECULAR ASPECTS OF SKELETAL MUSCLE ASSEMBLY AND FUNCTION

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National Institute of Arthritis and Musculoskeletal and Skin Diseases

INTRODUCTION

The Muscle Biology Program of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) supports research on skeletal muscle, its diseases and disorders. This includes studies on normal muscle structure, function, development, and homeostasis. NIAMS, through this Program Announcement, encourages submission of grant applications in the specific area of the dynamic molecular events that bring about and maintain the highly organized and regular structures of skeletal muscle.

BACKGROUND

Skeletal muscle is a major tissue of the human body, responsible for forty percent of total body weight in normal adults. Its primary function is generating and controlling body motion. Extensive observation and research, motivated by this major role, has enhanced our understanding of many aspects of muscle action. Major contractile, regulatory, and structural proteins have been isolated and characterized. The genetic sequences encoding many of these proteins are known and subject to current techniques of cloning and site-directed mutagenesis. Researchers are determining the mechanisms that control genetic expression. There are detailed studies on structure of regulatory, contractile, cytoskeletal, and membrane proteins. Electron micrographs and immunofluorescent light images reveal a regularly organized ultrastructure, the composition of which has not been completely determined. We can describe extensive changes in appearance and protein composition as muscle develops and differentiates. This knowledge provides the basis for studies on the molecular mechanisms which bring about and maintain the structure of the myofibril. Similarly, extensive knowledge of the molecular architecture of muscle structures, such as thick and thin filaments, provides the background for studies at the atomic level of the inter- molecular basis for both muscle force and myofibril stability.

There are major unknowns regarding the development and maintenance of myofibrils: proteins or structures that have not yet been isolated and characterized; the biologically significant mechanisms underlying the dynamics of protein assembly, organization and exchange; the mechanisms responsible for control of protein expression, which result in different compositions dependent on muscle activity; the ways extracellular matrix proteins, membrane proteins, and the cytoskeleton influence myofibrillar assembly, sites

of attachments and alignment; forces that stabilize the structures of the myofibrils, so that contractile force can be generated and controlled; and how proteins in these structures are replaced without impairing the contractile or metabolic activity of the muscles.

RESEARCH GOALS AND SCOPE

The primary goal of this Program Announcement is to foster research that enhances knowledge about the molecules of skeletal muscle and understanding of the molecular interactions that occur in the assembly and maintenance of striated muscle. This includes studies on individual processes as well as studies that try to integrate multidisciplinary approaches.

The scope of possible research areas includes, but is not limited to, the following topics:

1) Studies of genetic determinants and regulatory mechanisms important to myofibril assembly. This includes studies on influences of stimulation and hormonal environment, and the role of the multiple nuclei within individual muscle cells;

2) Studies of the role of extracellular matrix, cytoskeletal, and membrane proteins in myofibrillar organization;

3) Characterization of proteins and other molecules involved in establishing and maintaining myofibril structure. This includes non-muscle proteins when they present relevant models. Studies on mechanisms and dynamics of how these components interact to form multi-component complexes;

4) Studies of the structures visible within the myofibril, such as the thick and thin filaments, the I-Z-I complex, the myotendinous junction and other structures responsible for coordination of structure between filamentous bundles;

5) Characterization of the forces that stabilize structures and provide for regulation of myofibrillar function, including tension development;

6) Studies on mechanisms of homeostasis and repair, including myofibril remodelling and protein turnover and replacement within functional complexes; and

7) Studies of molecular changes in response to exercise and disease, with focus on molecular mechanisms of hypertrophy and atrophy, including the role of messengers and receptors on the cell surface.

Investigators are encouraged to use the full range of current disciplines and techniques, including biochemistry, biophysics, molecular genetics and recombinant techniques, and cell biology.

MECHANISM OF SUPPORT

Applicants may apply for research project grants (R01), program project awards (P01), FIRST awards and suitable fellowships or research career awards.

APPLICATION AND REVIEW PROCEDURES

Applications in response to this announcement will be reviewed in accordance with the usual Public Health Service peer review procedures. Review criteria include: significance and originality of the research goals and approaches; feasibility of the research and adequacy of the experimental design; training, research competence, and dedication of the investigator(s); adequacy of available facilities; and provision for the humane care of animals. Decisions will be based on initial review group and National Advisory Council recommendations.

Applications should be submitted on form PHS-398 (rev. 10/88) or the appropriate training/fellowship application form, available in the business or grants office at most academic or research institutions, or from the Division of Research Grants, National Institutes of Health, (301) 496-7441. Applications will be accepted in accordance with the submission dates for new applications on a continuing basis: February 1, June 1, October 1. Fellowship receipt dates are January 10, May 10, September 10.

Applicants are required to include, where feasible and appropriate, women as well as men and minorities in the study of populations for all clinical and research efforts and to analyze, where appropriate, differences between these populations. If women and minorities are not to be included, a clear rationale for their exclusion should be provided.

The phrase "RESPONSE TO NIAMS PROGRAM ANNOUNCEMENT: MOLECULAR ASPECTS OF SKELETAL MUSCLE ASSEMBLY AND FUNCTION, PA-90-34" should be typed on line 2 of the face page of the application. The original and six copies should be sent or delivered to:

Grant Application Receipt Office Division of Research Grants Westwood Building, Room 240 National Institutes of Health Bethesda, MD 20892-4500**

For further information, investigators are encouraged to contact the following individual:

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This program is described in the Catalog of Federal Domestic Assistance No.13.846, Arthritis and Musculoskeletal and Skin Diseases Research. Awards will be made under the authority of the Public Health Service Act, administered under PHS grant policies and Federal Regulations 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

**THE MAILING ADDRESS GIVEN FOR SENDING APPLICATIONS TO THE DIVISION OF RESEARCH GRANTS OR CONTACTING PROGRAM STAFF IN THE WESTWOOD BUILDING IS THE CENTRAL MAILING ADDRESS FOR THE NATIONAL INSTITUTES OF HEALTH. APPLICANTS WHO USE EXPRESS MAIL OR A COURIER SERVICE ARE ADVISED TO FOLLOW THE CARRIER'S REQUIREMENTS FOR SHOWING A STREET ADDRESS. THE ADDRESS FOR THE WESTWOOD BUILDING IS:

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